Remarks

Claims 1-34 and 44-48 remain pending in the present application. Claims 35-43 were previously cancelled. New claims 49-54 have been added. Claims 49 and 50 parallel originally pending claims 1 and 33, save for the addition of a new step (ii) requiring that the test sample be treated under a condition sufficient to lyse contaminating mycoplasma but insufficient to lyse bacterial cells. Support for this amendment is found, *inter alia,* at page 10, line 12 to page 11, line 5 of the pending specification. New claims 51-54 also parallel originally pending claims 1, 2, 3 and 33 save for the addition of a new step requiring that the test sample be filtered to remove bacterial cells. Support for this amendment is found, *inter alia,* at page 11, lines 12 to 21 of the specification.

Applicants do not believe any of these amendments introduce new matter into the application. Applicants respectfully request reconsideration and allowance of the claims in light of the following remarks.

Claims 1-24, 33, 44 have been rejected under 35 U.S.C. 112, first paragraph as being enabled only for detecting the presence of contaminating *mycoplasma* in a mammalian cell culture. This rejection is respectfully traversed.

In making this rejection the Office Action contends that the specification "does not reasonably provide enablement for any test samples with bacteria and certain eukaryotic microbes growth (such as fungi, see Ingram-Smith et al., Trends in Microbiology, 2006:14(6):249-253)." Ignoring that the cited reference admits that "these enzymatic activities have not yet been demonstrated in eukaryotic microbes" (see page 252, right hand column, lines 18-19), we fail to see how the potential interference from other microbes impacts the enablement of the pending claims.

In the first place, the rejection apparently is based solely on the assumption that the presence of bacteria or eukaryotic microbes in a sample would render the claimed method inoperative. No evidence is cited and the assumption is based only on the Examiner's speculation. Indeed, the evidence in the specification is to the contrary. The specification demonstrates that the method can be practiced in the presence of bacteria and in that circumstance can successfully identify *mycoplasma* contamination. See especially Example 7, pages 29-32, including Figures 10 and 11. Indeed, the application on several occasions teaches techniques for analyzing samples containing bacteria, *inter alia,* see page 10, line 12 to page 13, line 5. To the extent there are other microbes that could potentially complicate the assay method, one skilled in the art recognizes that the techniques for accommodating them would be the same as those used for bacteria.

Secondly, even if the presence of another microbe in a sample caused a positive result in the test (presumably because the other microbe contains an active enzyme with a similar activity to the *mycoplasma* enzymes sought to be detected), the potential generation of such a possible "false positive" result is not indicative of a lack of enablement of the claimed invention. False positive results are a potential result in many assays and are not indicative that an assay is either non-enabled or inoperative. Such results are a fact of life and can be dealt with a variety of ways, some of which are described in the specification. In any event, there is no evidence of record showing that any *mycoplasma* present in the tested sample would not similarly be detected, *i.e.,* that the presence of other microbes would prevent the detection of *mycoplasma* if present. The only potential drawback is that in that particular test one might not be certain of the

cause for the result. That complication, however, does not amount to a lack of enablement.

Finally, pending claim 6 (original) and new claims 49-54 affirmatively require a treatment step that would at a minimum reduce, and for the most part likely eliminate, the complication or incidence of such false positive results. See Schramm and Weyens-van Witzenberg 1989; Stanley 1989; Pellegrini *et al* 1992 and Baseman and Tully 1997, each of which was cited in the Information Disclosure Statement filed August 26, 2004. In this regard, applicant was unable to find an explanation in the Office Action why original claim 6 was included in the lack of enablement rejection. Applicant again submits that treatment protocols that are insufficient to lyse the cell walls of bacterial cells would be equally unable to lyse the cell walls of other microbes, such as yeasts and fungi, that the Office Action has identified as support for the rejection.

All of the previously pending claims also stand rejected as being unpatentable (obvious) under 35 U.S.C. 103(a) over the combination of Kahane et al., (FEMS Microbiology Letters 1978;3:143-145) (hereafter "Kahane") in view of Ito et al., (Analytical Sciences 2003;19:105-109) (hereafter "Ito"). This rejection is respectfully traversed.

The claims are directed to detecting the presence of contaminating *mycoplasma* in a sample. By using the terms "contaminating," "contaminated," or "contamination" in the claims in connection with *mycoplasma*, it is understood that the sample is one in which it is not known whether or not it contains any *mycoplasma* and further any *mycoplasma* in the sample is likely to be present in a small amount. Claim 32 recites a method for treating a cell culture to remove the *mycoplasma* contamination. Claim 33

specifically requires the use of a bioluminescent reaction in the detecting or measurement step. New claims 49-54 are similarly focused.

The primary reference, Kahane, is essentially an academic article relating to the identification and biochemical characterization of acetate kinase in pure *mycoplasma* cultures. In particular, Kahane presents the results of a study aimed at determining whether (assessing the hypothesis that) acetate kinase (AK) acts as a supplier of ATP in *mycoplasma* as it does in anaerobic bacteria. In this regard, Kahane thus describes a method for the isolation and the analysis of AK. The reference obtains a pure preparation of AK from a known source, *A. laidlawii*. Thus, the organism was specifically cultured for producing the enzyme which was purified therefrom for analysis.

The method employed by Kahane is actually relatively crude, as it uses an enzyme-coupled (*i.e.,* two-step) detection system and therefore requires a relatively large amount of *mycoplasma* in order to detect any acetate kinase activity at all. Given that circumstance, a skilled worker would never have considered the teachings of Kahane in the context of developing a method for detecting small amounts of contaminating *mycoplasma* in a sample.

Kahane has no need to analyze any particular sample to detect whether *mycoplasma* is present in the sample. Rather, Kahane specifically cultured an organism known to be a source of the enzyme for the sole purpose of preparing a purified preparation of the enzyme for analysis simply to test the hypothesis on the role played by AK. The Office Action accordingly acknowledges that Kahane does not teach the detection of *mycoplasma* in cell culture (see page 4, lines 12-13 of the Office Action).

Nonetheless, the Office Action suggests that Kahane is cited [solely?] "for teaching an acetate kinase assay and establishing acetate kinase's presence in mycoplasma." (page 5 of Office Action). But as explained above, given the circumstances surrounding Kahane's assay, a skilled worker would never have considered its teachings in the context of developing a method for detecting small amounts of contaminating *mycoplasma* in a sample. Kahane needed a large quantity of *mycoplasma* and knew it was there. Only through a hindsight evaluation of Kahane, *i.e.,* only with the pre-existing knowledge of the present invention, would a skilled worker have had any reason to consult Kahane's teachings. Indeed, the fact that Kahane's teaching were published almost thirty (30) years prior to applicant's invention belies the position taken in the Office Action.

As the secondary reference, the Office Action relies on Ito. Ito relates to a bioluminescent approach for simultaneously assessing acetate kinase (AK) and pyruvate phosphate dikinase (PPDK) activities. In particular, Ito uses acetate kinase activity as one of the enzymatic reporters in a tandem immunoassay for unrelated antigens (*e.g.,* for assaying insulin and C-peptide in the same sample). Ito used PPDK from *Microbisora rosea subsp. Aerata* and AK from *B. stearothermophilus.* Nothing in Ito links the acetate kinase to *mycoplasma.*

We question whether, in the absence of impermissible hindsight, a skilled worker would ever have considered Ito in combination with Kahane. As with Kahane, Ito has nothing to do with assessing the presence of contaminating *mycoplasma* in a sample. Nothing links these separate, disparate references besides the pending application and the attending claims. Nowhere in the rejection is there any explanation of why a skilled

worker would have been motivated, as a consequence of these reference, to develop an assay designed to assess mycoplasma contamination and why a skilled worker would have selected these references in that endeavor.

As the Federal Circuit cautioned in *In re Dembiczak*, 175 F.3d 994, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999), "[m]easuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." The fact finder must avoid the "insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against the teacher." *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988). Indeed, in its recent KSR decision (*KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007)), the Supreme Court also cautioned against using hindsight in the patentability analysis stating that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." We submit that the present rejection (1) ignores the real world situation of the inventive development and (2) uses hindsight both to select teachings from the prior art and to evaluate how those teachings might have been used by a skilled worker.

Indeed, even when Ito is considered with Kahane, the combination of these references does not suggest the claimed invention. At best, the skilled worker would simply consider Ito's bioluminescent assay as an alternative technique to use in the analysis of the role played by AK, *i.e.,* for measuring the activity of Kahane's pure acetate kinase (AK) preparation. However, Kahane's method of determining the activity

of a purified enzyme that has been purposely produced and is known to be present in the analyzed sample does not provide any hint of a method for assessing whether a sample has unknowingly been contaminated with *mycoplasma.*

Particularly lacking in the combination presented in the Office Action, for example, is (1) why a skilled worker presented with Kahane would need to run a control sample and compare the results of that control sample with a second measurement (see requirements of claim 2 and thus all of its dependent claims and claim 33), and (2) why a skilled worker would use the method of Kahane on a cell culture at all (see claims 25-29, and 45-48) and particularly in a method for treating a cell culture (claim 32).

Kahane provides no motivation to use its assay on any sample that is of unknown composition, *i.e.,* that is not already known to contain acetate kinase. If the sample does not knowingly contain acetate kinase, why would Kahane have any interest in testing it? Only by exercising a hindsight analysis of the claimed invention would a skilled worker see any possible nexus between Kahane's assay and the present invention.

Reconsideration and formal allowance of the pending claims thus are respectfully requested.

Respectfully submitted,

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